Health Update:

Data Suggest Declining Susceptibility to Cephalosporins Among *Neisseria gonorrhoeae* Isolates

July 12, 2011

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Health Update
July 12, 2011

FROM: **MARGARET T. DONNELLY**
DIRECTOR

SUBJECT: **Data Suggest Declining Susceptibility to Cephalosporins Among *Neisseria gonorrhoeae* Isolates**

On May 10, 2011, the Missouri Department of Health and Senior Services (DHSS) issued a Health Advisory entitled "New Guidelines for the Management of Sexually Transmitted Diseases",[1] which alerted medical providers to new treatment guidelines for sexually transmitted diseases (STDs) from the Centers for Disease Control and Prevention (CDC).[2] Included in these new guidelines, and briefly summarized in the Health Advisory, are revised treatment regimens for gonorrhea.

On July 8, 2011, the *Morbidity and Mortality Weekly Report* (*MMWR*) contained an article entitled "Cephalosporin Susceptibility Among *Neisseria gonorrhoeae* Isolates – United States, 2000-2010."[3] This article presents data which suggest declining susceptibility to cephalosporins – the only remaining class of antibiotics available to treat gonorrhea. This emphasizes the importance of current recommendations that call for dual therapy of gonorrhea with a cephalosporin PLUS either azithromycin or doxycycline. **Based on the findings reported in this *MMWR* article, CDC is now recommending ceftriaxone 250 mg intramuscularly PLUS azithromycin 1 g orally as the most effective treatment for uncomplicated gonorrhea.**

Known or suspected cases of gonorrhea should be reported to the local public health agency (LPHA), or to DHSS at 573/751-6439. In addition, medical providers should be vigilant for treatment failure and report its occurrence to the LPHA, or to DHSS, within 24 hours.

For the *MMWR* article,[3] researchers analyzed 10 years of gonorrhea isolates from male patients in 30 U.S. cities collected through CDC's Gonococcal Isolate Surveillance Project (GISP). The analysis showed an increase in the proportion of isolates with elevated minimum inhibitory concentrations (MICs), the lowest concentration of an antibiotic that inhibits visible growth of the bacteria. Increases in MICs suggest declining antibiotic susceptibility. From 2000-2010, the percentage of isolates exhibiting elevated MICs rose from 0.2% - 1.4% of isolates for cefixime and from 0.1% - 0.3% for ceftriaxone.

The article includes the following comments and recommendations (slightly edited, and including Missouri-specific information):

- The epidemiologic pattern of cephalosporin susceptibility . . . . is similar to that previously observed during the emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the U.S. Although the history of fluoroquinolone-resistant *N. gonorrhoeae* might not predict the patterns of decreasing cephalosporin susceptibility, the observed trends are concerning even though the current prevalence of isolates with elevated MICs remains low overall.

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1. DHSS *Health Advisory: New Guidelines for the Management of Sexually Transmitted Diseases*, May 10, 2011. http://health.mo.gov/emergencies/ert/alertsadvisories/pdf/had51011.pdf

2. CDC. *2010 STD Treatment Guidelines*. http://www.cdc.gov/std/treatment/2010/default.htm

3. CDC. Cephalosporin Susceptibility Among Neisseria gonorrhoeae Isolates – United States, 2000-2010. *MMWR* 2011;60(26);873-7 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6026a2.htm?s_cid=mm6026a2_w

- Previously, the emergence and spread of gonococcal antibiotic resistance in the U.S. was addressed by changing the recommended antibiotics for treatment. However, no other well-studied and effective antibiotic treatment options or combinations currently are available other than those now being recommended. The emergence of gonococcal cephalosporin resistance would substantially limit available treatment options.

- In light of the diminished resources available to STD control programs and the past inability to prevent emergence of resistance, the eventual emergence of cephalosporin resistance appears likely. Actions undertaken now could delay the spread of cephalosporin-resistant strains and mitigate the public health consequences. Effective treatment of gonorrhea is essential and now requires two antibiotics.

- The findings in this report suggest that gonococcal resistance to cefixime might emerge in the U.S. before resistance to ceftriaxone. Ceftriaxone is the most effective cephalosporin for treatment of gonorrhea and should be used for treatment of gonorrhea in combination with azithromycin or doxycycline. Azithromycin is preferred over doxycycline for dual therapy with ceftriaxone; of the 2009-2010 isolates with decreased susceptibility to cefixime, none exhibited decreased susceptibility to azithromycin, and all of them exhibited tetracycline resistance.

- **Based on the findings in this report, CDC currently is recommending <u>ceftriaxone</u> 250 mg intramuscularly and <u>azithromycin</u> 1 g orally as the most effective treatment for uncomplicated gonorrhea.**

- In addition to effective treatment, prompt recognition of cephalosporin-resistant gonorrhea is critical. Clinicians should remain vigilant for treatment failures (evidenced by persistent symptoms or a positive follow-up test despite treatment) among patients treated for gonorrhea with CDC-recommended antibiotics and obtain specimens for gonococcal culture from patients with possible treatment failure. Clinicians caring for patients with gonorrhea, particularly men who have sex with men (MSM) in the western U.S., might consider having patients return 1 week after treatment for test-of-cure with culture, preferably, or with nucleic acid amplification tests (NAATs).

- If a patient experiences cefixime treatment failure, clinicians should re-treat the patient with 250 mg ceftriaxone intramuscularly and 2 g azithromycin orally. If a patient experiences a ceftriaxone treatment failure, clinicians should consult with an infectious disease expert and DHSS (573/751-6439) regarding re-treatment. These patients should return for tests-of-cure within 1 week, preferably with culture, or, if culture is not available, with NAAT. If the follow-up NAAT result is positive, a specimen for culture should be obtained. Clinicians also should ensure that the patient's sex partners from the preceding 2 months are tested for gonorrhea (preferably with culture) and empirically treated with ceftriaxone 250 mg intramuscularly and azithromycin 2 g orally. Finally, these treatment failures should be reported to DHSS within 24 hours.

- Laboratorians and clinicians are requested to report gonococcal isolates with decreased cefixime or ceftriaxone susceptibility ($\geq$0.5 μg/mL) to DHSS within 24 hours of identification. Isolates can be submitted to CDC's Neisseria Reference Laboratory for confirmation of susceptibility testing through the Missouri State Public Health Laboratory.

Questions and case reports can be directed to DHSS' Bureau of HIV, STD, and Hepatitis at 573/751-6439, or by faxing to 573/751-6417.

Health Update:

UPDATE to Emergency Room and Primary Care Providers' Reference Sheet on Ehrlichiosis and Tick-Borne Spotted Fever Illnesses

July 25, 2011

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Health Update
July 25, 2011

FROM: **MARGARET T. DONNELLY**
DIRECTOR

SUBJECT: **UPDATE to Emergency Room and Primary Care Providers' Reference Sheet on Ehrlichiosis and Tick-Borne Spotted Fever Illnesses**

Summary

The Missouri Department of Health and Senior Services (DHSS) alerts health care providers that reports of ehrlichiosis illnesses through July 12, 2011 are 21% higher than for the same period, on average, for the years 2006 through 2010. Ehrlichiosis is an acute infection similar in initial presentation to many viral and bacterial febrile illnesses, including Rocky Mountain spotted fever (RMSF). Peak transmission of tick-borne *Ehrlichia* species can continue into early August. Active transmission in Missouri typically is observed from late April through early October. As of July 12, 2011, reports of RMSF are not elevated in Missouri compared with activity observed over the previous five years.

Ehrlichiosis and RMSF are tick-borne rickettsial diseases (TBRD) transmitted primarily through the bites of the lone star and American dog tick, respectively. The rickettsial disease agents most frequently reported in Missouri are *Ehrlichia chaffeensis* (ehrlichiosis); *Ehrlichia ewingii* (ehrlichiosis); and *Rickettsia rickettsii* (RMSF).

Ehrlichiosis and RMSF can cause severe illness and death in otherwise healthy adults and children. Diagnosis of these illnesses must be made on the basis of clinical signs and symptoms, and can later be confirmed using specialized laboratory tests.

Delay in diagnosis and treatment is associated with more severe illness and death. Case-fatality rates for immunocompromised patients are characteristically higher than case-fatality rates reported for the general population. Care providers should include ehrlichiosis and spotted fevers in the differential diagnosis of summertime febrile patients with known or potential tick exposure, and/or who do not respond to antibiotic therapy.

Clinical presentation, diagnostic assessment, and antibiotic therapy for Missouri's TBRDs are summarized in the attached physicians' Reference Sheet. For detailed information, refer to: *Diagnosis and Management of Tick-borne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichioses, and Anaplasmosis, United States – A Practical Guide for Physicians and Other Health-Care and Public Health Professionals* at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm.

See the last page of the Reference Sheet for public health disease reporting guidance, and additional clinical references, on ehrlichiosis and RMSF.

Emergency Room and Primary Care Providers' Reference Sheet on Ehrlichiosis and Tick-Borne Spotted Fevers

Missouri Department of Health and Senior Services Updated July 2011

Tick-Borne Rickettsial Disease (TBRD) Agents Covered In This Reference Sheet

Ehrlichia chaffeensis (ehrlichiosis)
Ehrlichia ewingii (ehrlichiosis)
Anaplasma phagocytophilum (human anaplasmosis)
Rickettsia rickettsii (traditional Rocky Mountain spotted fever [RMSF])
Rickettsia parkeri (a newly recognized febrile, eschar-associated illness)

Clinical Presentation

- Ehrlichiosis and spotted fever illnesses can be difficult to distinguish from viral febrile infections.
- Most patients present during the first 2 to 4 days of illness when serologic detection is unlikely.
- Onset is frequently rapid; the majority of patients experience high fever, shaking chills, severe headache, and generalized myalgias or arthralgias.
- Some patients, especially children, suffer early from nausea, vomiting, and anorexia.
- The diagnosis of ehrlichiosis and RMSF must be made based on clinical signs and symptoms, and can later be confirmed using specialized laboratory tests.
- The majority of reported cases of ehrlichiosis and traditional RMSF require hospitalization.
  - Manifestations of ehrlichiosis due to *E. ewingii* generally are less severe than infection with *E. chaffeensis*.
  - Newly described rickettsial illness due to ***R. parkeri*** has manifestations similar to RMSF, but is a milder illness. Because it is usually associated with an eschar, it can also resemble rickettsialpox.
  - Anaplasmosis in Missouri patients is linked to travel in the upper Midwest or New England states.

Rash – Presentation Varies with Infecting Agent

- Ehrlichiosis:
  - Rash is described in up to two-thirds of children infected with *E. chaffeensis*[1], but is less common in adults.
  - Can be transient; typically late in the course of disease.
  - Varies in character from petechial or maculopapular to diffuse erythema.
- RMSF
  - The classic spotted or generalized petechial rash of *R. rickettsii* is absent in about 10% of patients.
  - Rash is non-itchy and usually not apparent until day 5 or 6 of illness.
  - Rash on the palms and soles usually does not appear until late in the illness.
- *R. parkeri* eschar(s) or eruptions[2]
  - Infected tick bites, 0.5 - 1.5 cm wide, with a central area of ulcerated or scabbed skin surrounded by a halo of erythema (see photos at http://cid.oxfordjournals.org/content/47/9/1188.long).
  - Also have been observed as a maculopapular or papulovesicular eruption on the trunk and extremities, occasionally involving the palms and soles.
  - Obtain skin biopsy or swab for PCR analysis – for submission instructions and a link to the submission form, go to http://health.mo.gov/lab/virology/pdf/rickettsial_instructions.pdf, or call (573)751-3334.

Routine Laboratory Tests

- Ehrlichiosis: Important findings
  - Low platelet count (thrombocytopenia), low white blood cell count (leukopenia), and elevated levels of hepatic transaminases.
  - In CSF: mild lymphocytic pleocytosis (<250 cells/mm^3), elevated protein levels, and absence of low glucose levels (compared with other bacterial meningitides).
- RMSF: Findings in RMSF patients include normal white cell count with left shift, anemia, thrombocytopenia in severe cases, and hyponatremia. Increase in serum LDH and creatine kinase can also be observed due to diffuse tissue injury.

Tick Exposure Assessment

- Perform a detailed history for occupational, recreational, and residential exposure to ticks.
- Incubation period is five to ten days following a tick bite; tick attachment is often not recalled.

Serologic Diagnostic Tests

- Assessment is complicated by presence of antibodies, even in healthy populations, in endemic areas; persistence of some antibodies for years after the previous infection; and cross-reactivity in conventional serological assays.

- .Antibodies (IgM *and* IgG) via IFA are not yet detectable when most patients present.
  - IgG is sometimes detectable before IgM.
  - Increased IFA serology sensitivity with illness of seven to ten days.
  - IFA estimated at 94-100% sensitive at >14 days of illness.
  - Serological diagnosis can be considered confirmed only by a four-fold change of IgG-specific antibody titer by IFA between paired serum samples (second sample taken 2-4 weeks later).
- Never delay treatment decisions while waiting for laboratory confirmation of a diagnosis.

PCR Detection of Pathogen DNA

- PCR on an appropriate blood specimen, or on skin tissue, can identify DNA from the infecting bacteria; but the result may not be timely.
- Whole blood is useful for detecting *Ehrlichia* species by PCR because of the pathogen's tropism for circulating white blood cells.
- PCR is more sensitive in a biopsy or swab sample of the spotted rash or eschar than in an acute blood sample. (Spotted fever group rickettsial disease agents exhibit a tropism for epithelial cells.)

Diagnosis Confirmation

- Paired acute and convalescent serology and/or PCR assay to retrospectively confirm a diagnosis can be obtained at no charge through the Missouri State Public Health Laboratory.
- Specimen submission instructions and a link to the submission form are available at http://health.mo.gov/lab/virology/pdf/rickettsial_instructions.pdf, or call (573) 751-3334.

Treatment

- Treatment decisions are empirical – based on epidemiologic and clinical clues.
- Doxycycline is the drug of choice for TBRD infections in adults *and* children of any age
  - TBRDs can be life-threatening.
  - Available data suggest that courses of doxycycline <14 days do not cause significant discoloration of permanent teeth.[3]
- Refer to http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm for dosing and management of patients with clinical manifestations of TBRD.
- **Include ehrlichiosis and spotted fevers in the differential diagnosis of summertime febrile patients with known or potential tick exposure, and/or who do not respond to antibiotic therapy.**

Clinical Consequences/Sequelae

- Severe and life-threatening damage can occur in various organs in the body, to the skin, or to the nervous system during the initial phase of the infection when the bacteria are actively spreading.
- Permanent or long-term sequelae have been reported in the medical literature in people who were severely ill with ehrlichiosis and tick-borne spotted fevers (e.g., people hospitalized with the illness).

Public Health Disease Reporting

- Ehrlichiosis and RMSF (also known as a "spotted fever rickettsiosis") are reportable conditions in Missouri.
- Fax positive laboratory reports and case report forms to your local public health agency (LPHA), or to (573) 526-0235. Cases can also be reported by phone to your LPHA, or to the Missouri Department of Health and Senior Services at (573) 751-6113.

References

1. CDC. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis — United States: a practical guide for physicians and other health-care and public health professionals. *MMWR* 2006;55(No. RR-4). http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5504a1.htm
2. *Rickettsia parkeri* rickettsiosis and its clinical distinction from Rocky Mountain spotted fever. Paddock CD, et al. *Clinical Infectious Diseases*, 2008;47:1188-96. http://cid.oxfordjournals.org/content/47/9/1188.long.
3. Absence of Tooth Staining With Doxycycline Treatment in Young Children. Volovitz B., et al. *Clinical Pediatrics*, 2007;46:121-6. http://cpj.sagepub.com/content/46/2/121.abstract (subscription required).

Health Update:

Plak-Vac Oral Care System

November 10, 2011

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Health Update
November 10, 2011

FROM: **MARGARET T. DONNELLY**
DIRECTOR

SUBJECT: **Plak-Vac Oral Care System**

On October 21, 2011, the Missouri Department of Health and Senior Services (DHSS) issued a Health Alert (http://health.mo.gov/emergencies/ert/alertsadvisories/pdf/HA-BCepacia.pdf) advising health care facilities to temporarily suspend the use of Plak-Vac Oral Care System due to contamination with *Burkholderia cepacia* The distributor of this product issued a product recall on October 25, 2011, and notified its customers by letter on October 27, 2011. This Health Update provides additional information on the recall.

This recall affects only the lot numbers shown below. The distributor and manufacturer of the Plak-Vac Oral Care System have been working with the U.S. Food and Drug Administration (FDA) to assure that all remaining product is acceptable for patient use.

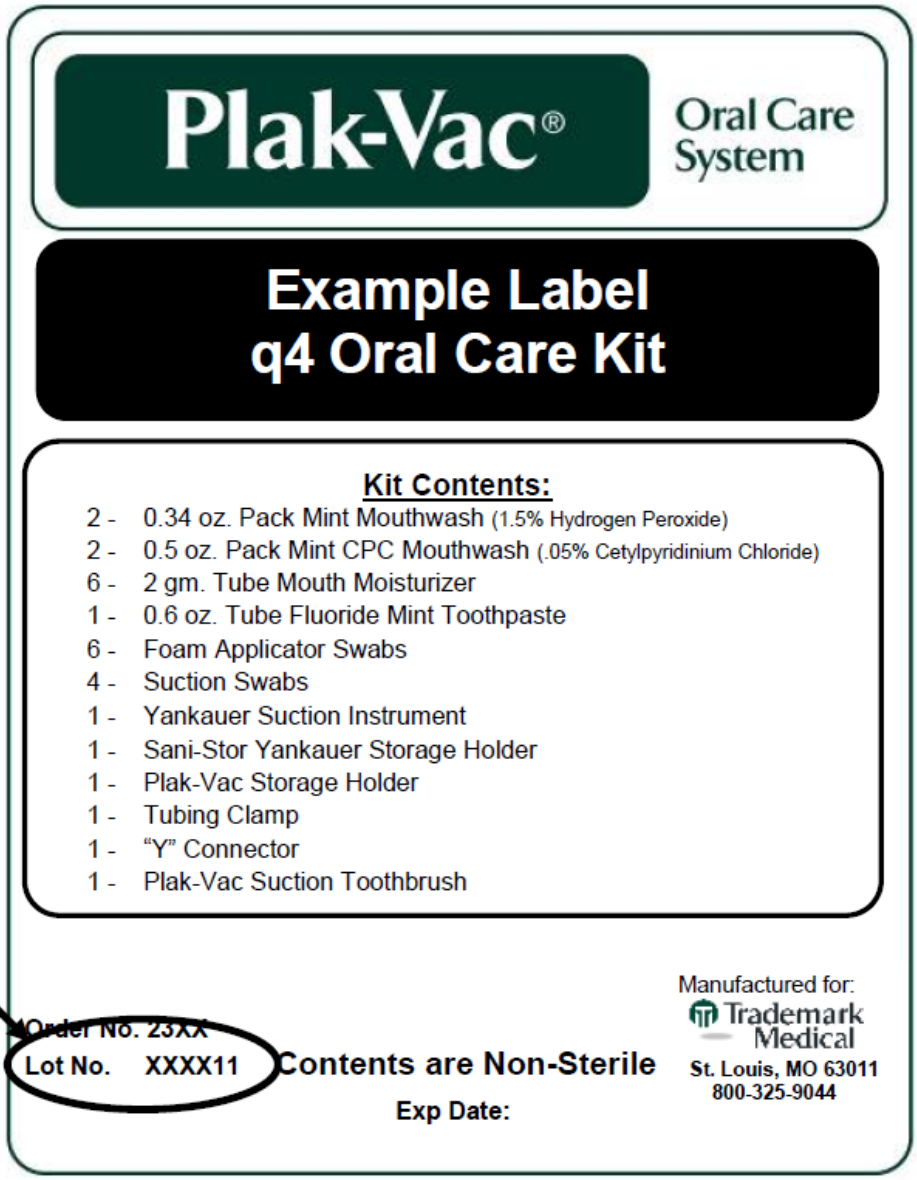
Recalled Lots: Lot numbers are located at the lower left hand corner of the main kit label, or on the lower right hand corner of the box label (see pages 2 and 3 for examples taken from the distributor's recall letter). These kits contain cetylpyridinium chloride (CPC) mouthwash packets that are marked with Lot Number 13068. Please contact your distributor if you still have any of these lots in your facility.

Kit # Lot #
- 2329 0390016-090711
- 2329 0390963-101111
- 2358 092711
- 2358 0390016-090711
- 2358 0390077-090811
- 2330A 082611
- 2330A 090611
- 2330A 091211
- 2330A 091411
- 2330A 091611
- 2330A 092611
- 2330A 092911
- 2336 389839
- 2381 101011
- 2460 092211

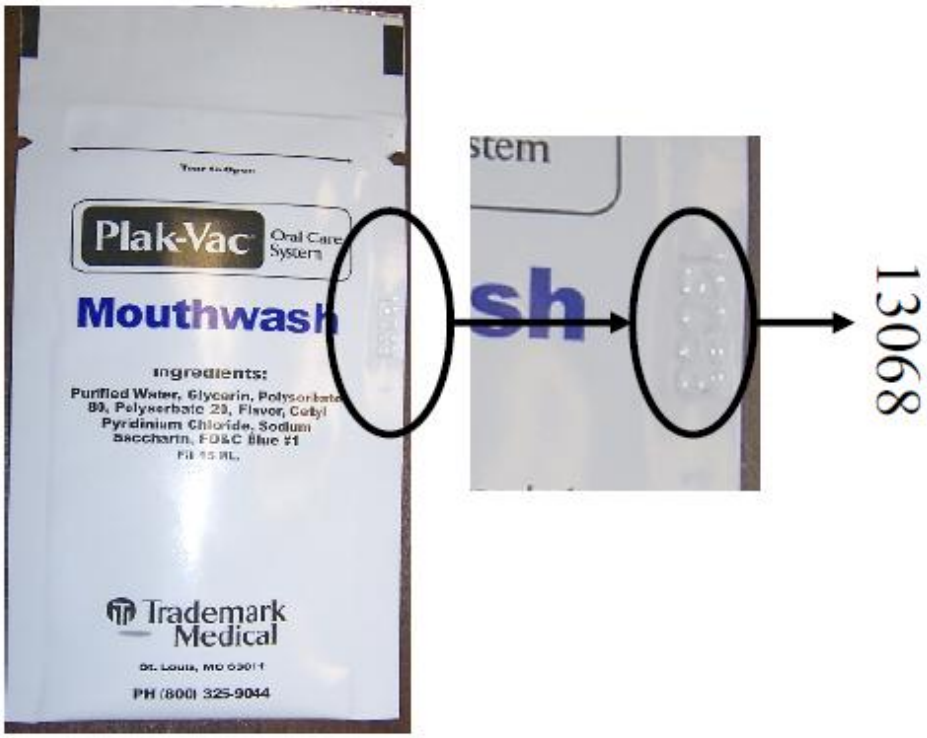
The distributor's recall letter is available at:
http://trademarkmedical.com/docs/Plak-Vac_Oral_Care_Kit_Recall_Notification_Web_Site_Posting.pdf .

Questions should be directed to DHSS' Section for Environmental Public Health at 573-751-6141.

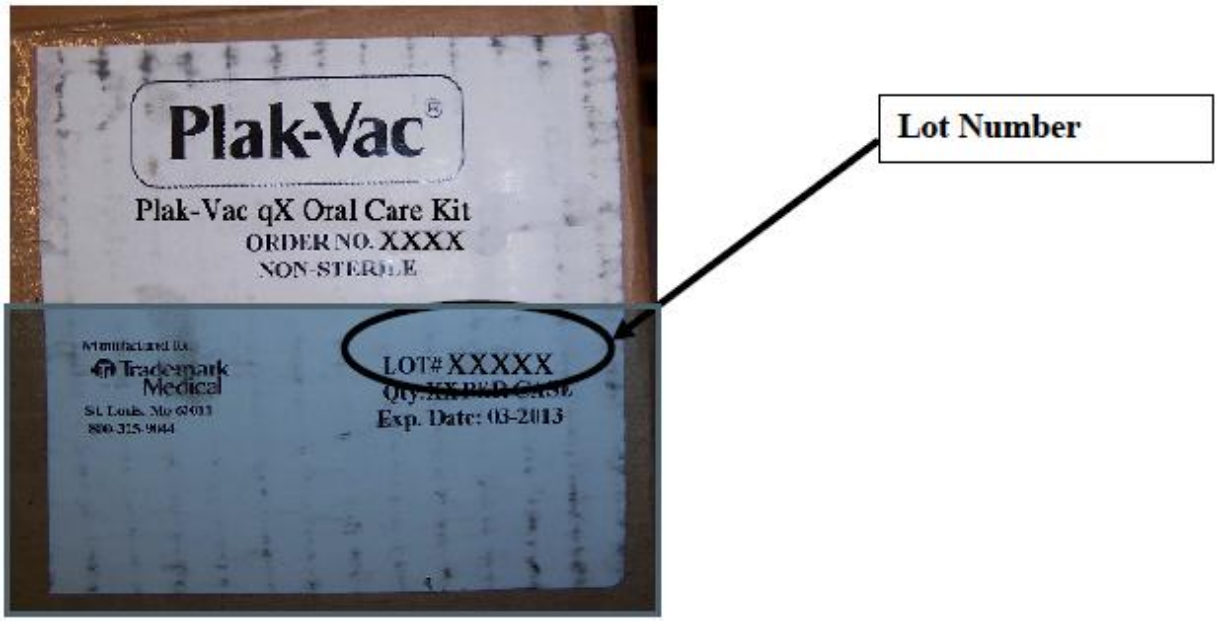
Example Kit Label



Example Mouthwash Packet



Example Box Label



Health Update:

Update: Two cases of invasive *Enterobacter sakazakii* infection in infants treated in Missouri hospitals

December 20, 2011

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Health Update
December 20, 2011

FROM: **MARGARET T. DONNELLY**
DIRECTOR

SUBJECT: **Update: Two cases of invasive *Enterobacter sakazakii* infection in infants treated in Missouri hospitals**

The Missouri Department of Health and Senior Services (DHSS) has received questions from Women, Infants, and Children (WIC) providers and physicians concerning the use of powdered formula following the December 19, 2011, Health Alert concerning invasive *Enterobacter sakazakii* infections in two infants treated in Missouri hospitals. For clarification, the powdered formula being tested for the bacteria is not a WIC approved formula. No formula offered by the WIC program has been implicated in the investigation.

As a reminder, when reconstituting powdered formula, it is recommended that the water be brought to a boil for two minutes and then let cool before mixing the formula. This procedure should be followed regardless of the water source. The following link provides guidelines for infant formula preparation: http://health.mo.gov/living/families/wic/wiclwp/pdf/InfantFormulaFactSheetEnglish.pdf.

The December 19, 2011, Health Alert on the *Enterobacter sakazakii* infections is available at: http://health.mo.gov/emergencies/ert/alertsadvisories/pdf/HA-Enterobacter121911.pdf

Questions should be directed to DHSS' Bureau of Communicable Disease Control and Prevention at 800/392-0272 (24/7).